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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,410	03/20/2001	Rudi Scherhag	0480/01227	1484

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EXAMINER	
SNEDDEN, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,410	SCHERHAG ET AL.	
	Examiner	Art Unit	
	Sheridan K Snedden	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5 and 8-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5 and 8-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. This Office Action is in response to Paper filed 24 September 2003. Claims 2, 3, and 7 have been canceled. Applicant's amendment of claims 1, 4, 5, and 8-12 is acknowledged. Applicant's addition of new claims 13-21 is acknowledged. Claims 1, 4, 5, and 8-21 are under examination.

Withdrawal of Objections and Rejections

2. The objections and/or rejections not explicitly restated or stated below are withdrawn.

Maintained Objections and Rejections

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 4-5 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Kurfuerst *et al.* (US Patent 5,663,141). Kurfuerst *et al.* teach a method of preventing coagulation of blood by administration to a host a PEG-hirudin conjugate (see claim 13; regarding claim 1). Kurfuerst *et al.* teach that the PEG-hirudin are useful for the prophylaxis of thromboembolic disease and for extracorporeal circulation, e.g. hemodialysis (see column 5, lines 30-52; regarding claim 2). Kurfuerst *et al.* teach that the compounds are administered as a daily dose

between 20 to 40,000 ATU/kg body weight (see column 5, lines 55-60; regarding claim 3). Kurfuerst *et al.* teach that the PEG-hirudin conjugates are superior to hirudin and heparin due to the prolonged biological activity (half-life), better bioavailability, and lower antigenicity (see column 5, lines 30-52). As such, the PEG-hirudin conjugates taught by Kurfuerst *et al.* display the 'enduring' activity necessitated in claim 5 and possess the inherent characteristic of a half-life of about 4 hours (regarding claim 4). The PEG-hirudin conjugate taught by Kurfuerst *et al.* is recombinant (see Example 1; regarding claim 12). Thus, the reference anticipates the claimed invention.

5. Applicant argues that the method of Kurfuerst *et al.* is not identical to the claimed method. Applicant distinguishes the present claims from the teaching of Kurfuerst *et al.* by the requirement that PEG-hirudin is applied during the extracorporeal phase of an intermittent hemodialysis therapy. As Kurfuerst *et al.* clearly teaches that PEG-hirudin is useful for the therapy and prophylaxis of thromboembolic disease and for extracorporeal circulation, e.g. hemodialysis (column 5, line 39-43), this argument implies that "chronic intermittent hemodialysis," or CIHD, therapy is the novel contribution of the present invention. However, as stated by Sussman *et al.* (column 2, line 67), CIHD is the most widely used form of hemodialysis and would thus be inherent in the teachings of Kurfuerst *et al.* The addition of "chronic renal insufficiency" into claim 1 does not overcome the teachings of Kurfuerst *et al.* as this would be the most common reason for someone to undergo CIHD, and thus, this teaching is also inherent in the teachings of Kurfuerst *et al.* As such, Applicant's arguments are unpersuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-5 and 7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kurfuerst *et al.* (US Patent 5,663,141) in view of Maraganore *et al.* (US Patent 5,256,559), De Rosa *et al.* (US Patent 5,723,576) and Fischer *et al.* (Kidney Int Suppl. 1999 Nov;72:S46-50).

Kurfuerst *et al.* teach a method of preventing coagulation of blood by administration to a host a PEG-hirudin conjugate (see claim 13; regarding claim 1). Kurfuerst *et al.* teach that the PEG-hirudin are useful for the prophylaxis of thromboembolic disease and for extracorporeal circulation, e.g. hemodialysis (see column 5, lines 30-52; regarding claim 2). Kurfuerst *et al.* teach that the compounds are administered as a daily dose between 20 to 40,000 ATU/kg body weight (see column 5, lines 55-60; regarding claim 3). Kurfuerst *et al.* teach that the PEG-hirudin conjugates are superior to hirudin and heparin due to the prolonged biological activity (half-life), better bioavailability, and lower antigenicity (see column 5, lines 30-52). As such, the PEG-hirudin conjugates taught by Kurfuerst *et al.* display the 'enduring' activity necessitated in claim 5 and possess the inherent characteristic of a half-life of about 4 hours (regarding claim 4). The PEG-hirudin conjugate taught by Kurfuerst *et al.* is recombinant (see Example 1; regarding claim 12).

Maraganore *et al.* teach the use of PEG-hirudin compositions which display the anticoagulant and platelet inhibitory activities for therapeutic and prophylactic purposes (see abstract, Example 12, column 9, lines 1-19). Inhibition of platelet aggregation may also be

desirable in extracorporeal treatments of blood, such as dialysis, storage of platelets in platelet concentrates and following certain surgical procedures, such as heart-lung bypass (see column 2, lines 1-9). The PEG-hirudin conjugates are administered to a host with a single dose (see column 10, lines 59-68). As such, the PEG-hirudin conjugates taught by Maraganore *et al* display the 'enduring' activity necessitated in claim 5 and possess the inherent characteristic of a half-life of about 4 hours (regarding claim 4; see example 12). Recomdinant DNA technologies may be utilized to supply the needed hirudin in order to make PEG-hirudin (see column 4, line 40).

De Rosa *et al.* teach the use of hirudin derivatives as an anticoagulant and antithrombotic agents (column 2, lines 4-5) useful for therapeutic, prophylactic and diagnostic applications. De Rosa *et al.* specifically teach the use of hirudin derivative compounds, in the prophylaxis of vascular complication such as arterial thrombosis, and specifically teach the use of the above compounds in extracorporeal circulation, particularly hemodialysis (column 7, lines 49-57). De Rosa *et al.* teach that the above compounds can be administered to a patient with the effective amount of 0.05 mg/kg to 250 mg/kg patient body weight per day (column 7, lines 19-37) and teach that administration of the anticoagulant hirudin derivates prolong APTT 250%, or 2.5 fold (column 10, line 60).

Kurfuerst *et al.* teaches that the PEG-hirudin has superior qualities to other anticoagulants, such as other hirudin and heparin derived compounds. Therefore, the teachings of Kurfuerst *et al.* would suggest and motivate one of ordinary skill in the art to substitute the PEG-hirudin compounds with other anticoagulants for use as prophylaxis of thromboembolic disease and for extracorporeal circulation (e.g. hemodialysis) as taught by Kurfuerst *et al.* and Maraganore *et al.*. Administration of anticoagulants, such as hirudin, heparin or PEG-hirudin, in

the form of a single dose prior to the start of hemodialysis is the standard of the prior art (regarding claims 8-9). Additionally, the anticoagulants are utilized in chronic treatments (regarding claims 7, 11). These standard protocols are exemplified by the teachings of Fischer *et al.* that demonstrate the single bolus of hirudin was use for patients undergoing continuous hemodialysis for treatment of chronic renal failure. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute hirudin in the treatment taught by Fischer *et al.* with PEG-hirudin as suggested by Kurfuerst *et al.* The teachings of De Rosa *et al.* indicate that the PEG-hirudin compounds would posses the inherent activity to prolong APTT by at least 2.5 fold (regarding claims 10-11). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

7. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the method of Kurfuerst *et al.* is not identical to the claimed method. Applicant distinguishes the present claims from the teaching of Kurfuerst *et al.* by the requirement that PEG-hirudin is applied during the extracorporeal phase of an intermittent hemodialysis therapy. As Kurfuerst *et al.* clearly teaches that PEG-hirudin is useful for the therapy and prophylaxis of thromboembolic disease and for extracorporeal circulation, e.g. hemodialysis (column 5, line 39-43), this argument implies that "chronic intermittent

hemodialysis," or CIHD, therapy is the novel contribution of the present invention. However, as stated by Sussman *et al.* (column 2, line 67), CIHD is the most widely used form of hemodialysis and would thus be inherent in the teachings of Kurfuerst *et al.* The addition of "chronic renal insufficiency" into claim 1 does not overcome the teachings of Kurfuerst *et al.* as this would be the most common reason for someone to undergo CIHD, and thus, this teaching is also inherent in the teachings of Kurfuerst *et al.*

To the teaching of Kurfuerst *et al.*, De Rosa *et al.*, Maraganore *et al.* and Fischer *et al.* teach the inherent properties of PEG-Hiruden and the obvious method steps and end points of the conducting chronic intermittent hemodialysis of a patient suffering from chronic renal insufficiency. As such, Applicant's arguments are unpersuasive.

New Rejections

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-5 and 8-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Bucha *et al.* (DE 199 15 862; see English equivalent CA 2 369 096). Bucha *et al.* teach PEG-hirudin as an anticoagulant for preventing thrombogenic effects during extracorporeal kidney replacement therapy, e.g. in chronic renal insufficiency, chronic glomerulonephritis, diabetic nephropathy or acute liver failure patients, using hemodialysis machines. Specifically, (PEG-hirudin) was used

as an anticoagulant in the hemodialysis treatment of a chronic glomerulonephritis patient, showing positive results in a heparin-induced thrombocytopenia Type II (HIT II) test. Heparin had previously been used as anticoagulant, but caused side-effects such as blood flow problems in the extremities, feeling cold, skin irritation and parasthesia. PEG-hirudin was administered as a bolus at 0.1 mg/kg for the first hemodialysis, 0.05 mg/kg for the second to eleventh hemodialyses and 0.025 mg/kg for subsequent hemodialyses. Monitoring was carried out using the Ecarin clotting time. The blood level of PEG-hirudin was 0.4 mu g/ml at the start of hemodialysis and 1.0 mu g/ml at the end. The pain-free distance (150-200 m during heparin-anticoagulated hemodialysis) was increased to more than 700 m after 10 hemodialyses, and increased further on continued treatment. Parasthetic disorders and nightly pain attacks were reduced after the first hemodialysis and completely eliminated after 7 hemodialyses. With this treatment, APTT would inherently be prolonged to at least 1.8. Thus, the reference anticipates the claimed invention.

Advisory Information

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (703) 305-4843. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-3975 for regular communications and (703) 746-3975 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
January 16, 2004

SKS

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER